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(54) Title: METHOD OF OBTAINING (22R) DIASTEREOISOMER OF BUDESONIDE

(57) Abstract

By the method according to the invention condensation of 11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 21-acetate with n-butyric aldehyde is carried out, in the known way, in the medium of hydrofluoric acid of concentration of 70-80 %. Theisolated crude condensation product is crystallized from ethanol and obtained 21-acetate of budesonide (22R) of at least 95 % content is hydrolyzed, and the product thus obtained is crystallized from ethyl acetate.

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Method of obtaining (22R) diastereoisomer of budesonide

The subject of the invention is a method of obtaining diastereoisomer of (22R) budesonide. Budesonide, i.e. (22R,S)-16α,17α-butylidenedioxy-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione is a mixture of diastereoisomers (22R) and (22S) differing in the position of an acetal chain (fig.1 and 2). Both compounds are active glucocorticoids applied in a mixture (1:1) in pharmaceutical forms: antiasthmatic aerosol or antiallergic ointment. (22R) diastereoisomer is 2-3 times more active pharmacologically than (22S) diastereoisomer [Brattsand R.; Eur.J.Res.Dis.63, suppl. 122,62-73 (1982)].

In pharmacotherapy a tendency is presently observed to apply optically active compounds and not racemic mixtures. In the case of budesonide both isomeric forms are pharmacologically active but their metabolism is different [Andersson P. et al.; Xenobiotica 17,35-44 (1987)]. Testing of action of a drug being a pure chemical individual is considerably easier than that of a mixture.

A known method of obtaining budesonide, that is a mixture of diastereoisomers (22R) and (22S) consists in condensation of 11β,16α,17α,21-tetrahydroxy-1,4-pregnadien-3,20-dione with n-butyric aldehyde in the presence of strong inorganic acids, e.g. perchloric acid, in organic solvents [FRG patent 2323216(1973)].

Those skilled in the art know also a method of obtaining a mixture of diastereoisomers (22R) and (22S), in which isomer (22R) is in majority, even up to 90%. The said method consists in condensation, discussed above, conducted in the presence of hydrofluoric acid of concentration of 48-70% or concentrated hydrochloric acid [Eur.pat.appln.164636 (28.05.85)].

According to th known method separation of a mixture of diastereoisomers (22R) and (22S) is carried out on a

column packed with Sephadex LH20 [Thalen A., Nylander B.: 19,247-266(1982)]. The said method requires the use of a very big amount of solvents and long separation time, and for these reasons it is technologically inconvenient, expensive and time-consuming.

Unexpectedly it has appeared out that the product obtained after condensation in the form of 21-acetate containing at least 80% of diastereoisomer (22R), after crystallization from ethanol, and then hydrolyzed and crystallized from ethyl acetate yields pure diastereoisomer (22R) with an admixture of diastereoisomer (22S) of 1% at the very most. The content of diastereoisomers is determined by the HPLC method. From post-crystallization filtrates containing a mixture of diastereoisomers of a composition of 8:2 or 7:3 one may separate budesonide 21-acetate, crystallize it again and after hydrolysis obtain pure diastereoisomer (22R).

By the method according to the invention condensation of 11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 21-acetate with n-butyric aldehyde is carried out, in the known way, in the medium of hydrofluoric acid of concentration of 70-80%. The isolated crude condensation product is crystallized from ethanol and obtained 21-acetate of budesonide (22R) of at least 95% content is hydrolyzed, and the product thus obtained is crystallized from ethyl acetate to obtain (22R) diastereoisomer of budesonide of at least 99% content.

An advantageous effect of the invention is that (22R) diastereoisomer of budesonide having the content of at least 99% is obtained at a yield of about 60%. The product obtained by the method according to the invention is an active substance of antiasthmatic aerosol and its content in a dose of 158 μg is equivalent to 200 μg of budesonide of a mixture (1:1) of diastereoisomers (22R and 22S). The method according to the invention is characterized by simplicity of procedure, enables saving organic solvents and is less labour-consuming.

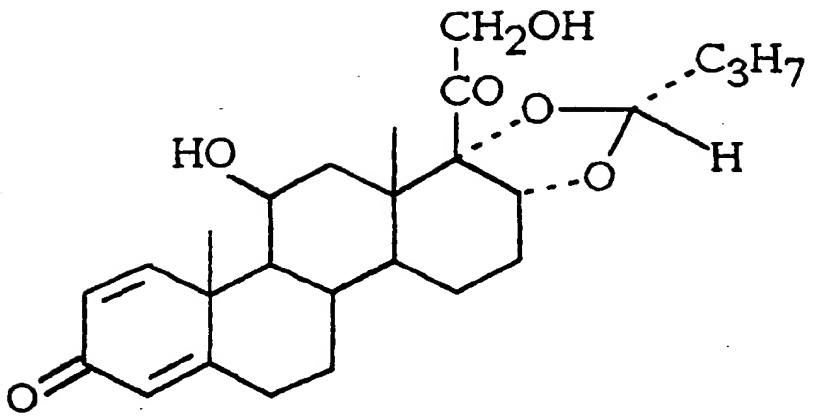
The after-mentioned example illustrates the invention without limiting its scope.

Example.

To a mixture of 7 ml of 75% hydrofluoric acid and 0.52 ml of n-butyric aldehyde, cooled to 0°C, 3.5 g of 11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 21-acetate is added in and stirred for 3 hours at maintenance of the temperature of 0°C. The obtained dark-red solution is poured into 50 ml of water with ice, neutralized by concentrated ammonia and extracted by chloroform. From the extract chloroform is distilled off under diminished pressure, and the residue is crystallized from ethanol. 2.2 g of 21-acetate of (22R) diastereoisomer of budesonide of $[\alpha]_D^{22}$+106°(c=1, CH_2Cl_2) is obtained, the content of 21-acetate of (22S) diastereoisomer of budesonide is 5%. The product is suspended in 40 ml of methanol, cooled to 0°C, 2.5 ml of 10% aquas solution of potassium carbonate is added thereto, and is stirred under nitrogen for 1 and 1/2 hours, at maintenance of the temperature of 0°C, after this it is neutralized with acetic acid, methanol is evaporated and (22R) diastereoisomer of budesonide is isolated either by filtering off or by extraction with chloroform. The separated product is crystallized from ethyl acetate and 1.7 g of (22R) diastereoisomer of budesonide is obtained, of melting point of 245-250°C (decomp.) $[\alpha]_D^{22}$+117.5°C (c=1, CH_2Cl_2); $a_{1cm}^{1\%}$ 350 at 242 nm. The content of (22S) diastereoisomer of budesonid determined by the the HPLC method is 1%.

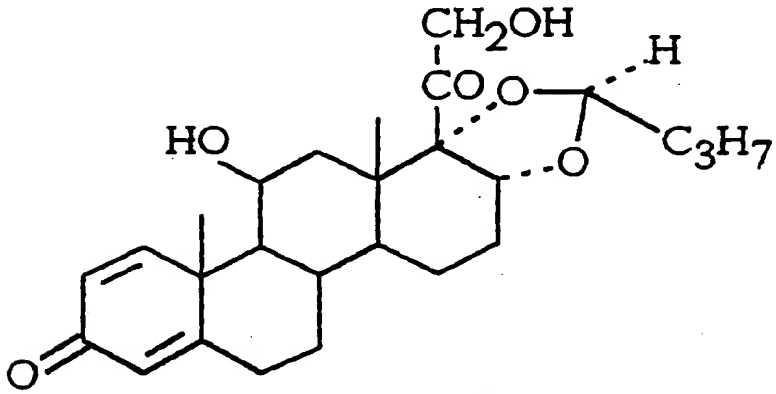
Patent claim

Method of obtaining of (22R) diastereoisomer of budesonide, consisting in a condensation reaction of 11β,16α,17α,21-tetra-hydroxy-1,4-pregnadiene-3,20-dione 21-acetate with n-butyric aldehyde conducted in the medium of hydrofluoric acid of concentration of 70-80%, characterized in that the isolated crude product of condensation is crystallized from ethanol and obtained 21-acetate of budesonide (22R) of at least 95% content is hydrolyzed, and the product thus obtained is crystallized from ethyl acetate.



(22R)

Fig. 1



(22S)

Fig. 2

INTERNATIONAL SEARCH REPORT

PCT/PL 91/00016

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07J71/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07J

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 164 636 (SICOR SOCIETA ITALIANA CORTICOSTEROIDI S.P.A.) 18 December 1985 cited in the application see page 8; example 1	1
A	US,A,3 996 359 (AB BOFORS) 7 December 1976 see the whole document	1

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16 MARCH 1992	24.03.92
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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PL 9100016 SA 54730

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP-A- 61040299	26-02-86
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